Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated August 24, 2007 (hereinafter, the "Final Action"). Claims 16, 22, 31-33, 42 and 44-47 are pending upon entry of the present Amendment. Applicants respectfully submit that no new matter is introduced by these claim amendments, as will be discussed in detail below, and Applicants respectfully request entry of these amendments.

Applicants further respectfully submit that the present application is in condition for allowance for at least the reasons set forth below.

I. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 16, 22, 31-33, 42 and 43 stand rejected under 35 U.S.C. §112, first paragraph, as lacking written description. *See* Final Action, page 2. More specifically, the Final Action regards this rejection as a new matter rejection in view of the recitation "prior to." *See* Final Action, pages 2 and 3.

Applicants respectfully disagree and submit that newly added claim recitations can be supported in the specification through **express, implicit, or inherent disclosure**. *See* "Written Description" Requirement as published on January 5, 2001 in the Federal Register (Vol. 66, pages 1099-1111), page 1105, first column of the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 (Emphasis Added). However, in an effort to expedite allowance of the present application, Applicants have amended Claims 16, 31 and 32 to delete this recitation. Accordingly, Applicants respectfully submit that this rejection has been obviated, and Applicants respectfully request that the written description rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. §103 (Obviousness)

Claims 16, 22, 31-33, 42 and 43 stand rejected under 35 U.S.C. § 103 as being obvious in view of Silvestris et al. *Ann Hematol.* **70(6)**: 313-318 (1995) or Bukowski et al. *Blood* **84 (10 Supp. 1):** 129A (1994) in view of JP 02 096535 to Chugai Pharm. Co. Ltd. for reasons previously made of record. *See* Final Action, page 3. Generally, the Final Action asserts the following:

> One of skill in the art would have found it obvious to try administering EPO prior to chemotherapy because it would either eliminate anemia or drastically reduce the severity of anemia. The skilled artisan would have good reason to pursue the available options of either administering EPO before or after chemotherapy because those of skill in the art routinely administer drugs to either prevent complications or lower the severity of any complications of chemotherapy. As a result of those of skill in the art administering EPO prior to chemotherapy, they would also indirectly provide an endothelial cell protecting amount to patients. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."
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> Final Action, page 5, citation omitted.

As acknowledged in the Final Action (*see* page 3), Applicants have previously submitted arguments and evidence in support thereof that it was not routine for those of skill in the art to administer erythropoietin (EPO) prior to the treatment of chemotherapy, but rather those receiving EPO were provided such treatment as a result of chemotherapy-induced anemia. *See also* Applicants' previous response filed October 28, 2005 and the concurrently filed Declaration under 37 C.F.R. §1.132 of Dr. George Sigounas. Applicants respectfully submit that such practice of providing EPO to patients was not routine at the time of filing the present application at least because those skilled in the art were apprised of the potential detrimental effects of providing EPO prophylactically as suggested by the Examiner. As recognized by one skilled in the art, the risk of detrimental effects of death, thrombosis and stroke that can be associated with attempting to increase hematocrit levels in patients who do not suffer from anemia far outweighed the benefit of preventing anemia. Accordingly, EPO was provided to chemotherapy patients **after** being diagnosed with anemia and not before, i.e., not prophylactically. In fact, even now in view of the risks, prophylactic administration of EPO is not recommended. *See* U.S. Food and Drug Administration Statement of John K. Jenkins, M.D.[1], specifically, pages 3-6.

In a further effort to expedite allowance of the present application, Applicants have amended Claims 31 and 32 to include the recitations directed to the endothelial-protecting amount of erythropoietin being provided in a dosage in a range of about 750 Units per

[1] U.S. Food and Drug Administration Statement of John K. Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration before Committee on Ways and Means Subcommittee on Health, United States House of Representatives on June 26, 2007.

kilogram to about 2000 Units per kilogram. Support for these claim amendments can be found in the specification as originally filed, for example, the specification recites the following:

> As used herein, endothelial-inhibiting amounts of EPO refer to those dosages which enhance or increase the suppression of endothelial growth which would otherwise occur due to exposure to a chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium. Alternatively, an endothelial-inhibiting amount of EPO may be defined as those dosages which decrease the numbers of viable endothelial cells following exposure to the chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium; the decreased number of viable cells is in comparison to that which would be expected in the absence of EPO.

Present Application, page 6, lines 19-31.

> In the present methods, where it is desired to protect the endothelium from the endothelial damage and/or endothelial growth suppression caused by a chemotherapeutic agent, EPO is administered in an endothelial-protecting amount. Suitable endothelial-protecting dosages may range from about 100 U/kg to about 200 U/kg. In the present methods, where it is desired to enhance the endothelial damage and/or endothelial growth suppression caused by a chemotherapeutic agent, EPO is administered in an endothelial-inhibiting amount which may range from about 750 U/kg to about 2,000 U/kg.

Present Application, page 12, lines 26-37.

Thus, it is clear that embodiments of the present invention contemplate administration of EPO in a dosage that is in a range from about 100 Units per kilogram to about 200 Units per kilogram and about 750 Units per kilogram to about 2,000 Units per kilogram.

The cited references do not teach or suggest a dosage-dependent function of EPO as described by the Applicants in the specification, and as noted above. Moreover, the cited references do not describe a method of reducing endothelial injury in a subject, comprising administering an effective endothelial-protecting amount of erythropoietin to said subject in need thereof, wherein said endothelial injury is caused by a chemotherapeutic agent. In particular embodiments, erythropoietin is provided as a dosage in a range of about 100 Units per kilogram to 200 Units per kilogram and about 750 Units per kilogram to about 2000 Units per kilogram. The cited references further do not provide any reasonable expectation of success of achieving the claimed methods where the cited references direct one of ordinary

skill in the art to administer EPO to chemotherapy patients **after** being diagnosed with anemia. Applicants further submit that one of ordinary skill in the art could not merely optimize the dosages provided to chemotherapy patients to arrive at the present invention where there is no impetus to provide EPO other than to treat anemia. Before Applicants' discovery, there was generally **no** motivation to provide EPO to cancer patients other than to treat anemia, and to treat anemia only **after** initiation of chemotherapy at least in an effort to avoid potential detrimental effects of EPO treatment in non-anemic patients.

Thus, at least in view of the remarks and claim amendments, Applicants respectfully submit that Claims 16, 22, 31-33, 42 and 44-47 are not obvious in view of any combination of the cited references, and Applicants respectfully request that the obviousness rejection be withdrawn.

III. Information Disclosure Statement

Applicants submit concurrently herewith an IDS and accompanying documents. The accompanying documents are those that have been filed in an Opposition Proceeding in the European Patent Office (EPO) for corresponding European Patent No. 0933995 (European Patent Application No. 97940974.5). Applicants note that some of the references submitted with the IDS have been previously considered by the Examiner and are re-submitted in order to complete the record of documents as submitted in the EPO proceeding.

Applicants respectfully request consideration of these documents, and Applicants respectfully submit that the pending claims are patentable over the currently submitted documents at least in view of the reasons previously made of record and further in view of previously considered references.